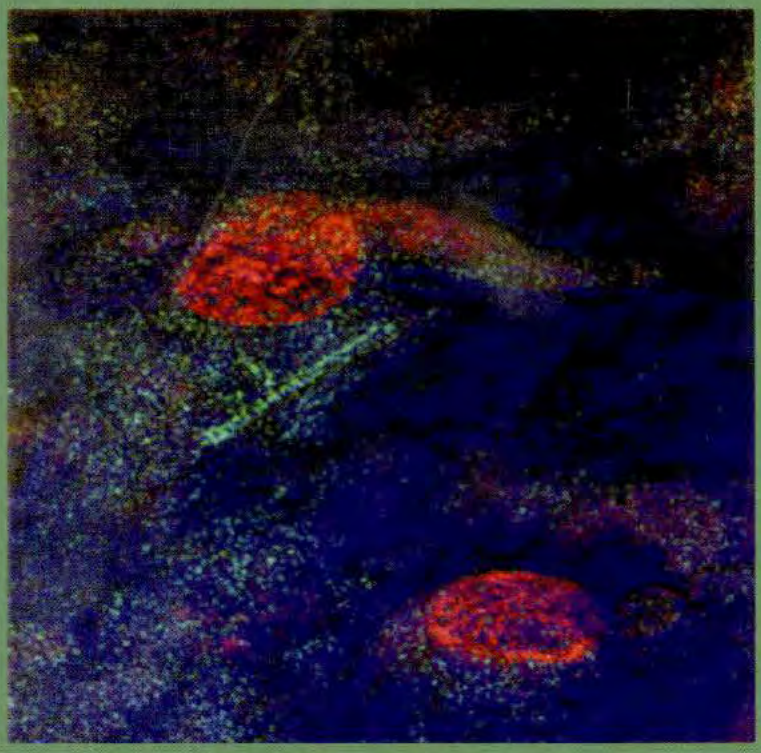
Exhibit 55

International Agency for Research on Cancer
World Health Organization

Mechanisms of Fibre Carcinogenesis



Edited by A.B. Kane, P. Boffetta, R. Saracci and J.D. Wilbourn

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International Agency For Research On Cancer

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The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

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Mechanisms of mineral fibre carcinogenesis

A.B. Kane

Introduction

Human diseases resulting from inhalation of fibres

The lower respiratory tract is the major target of inhaled particles and fibres with diameters less than or equal to 3 µm (McClellan *et al.*, 1992). The adverse health effects of inhaled fibres were first recognized in asbestos workers and people living in the vicinity of asbestos mines. Asbestos-related diseases were described in isolated case reports, beginning with asbestosis in 1924, and were followed by cohort mortality studies of lung cancer published by R. Doll in 1955 and malignant mesothelioma published by J.C. Wagner and co-workers in 1960 (for an historical review see Gordon, 1992).

The human diseases associated with exposure to asbestos fibres are summarized in Table 1. The conducting airways of the respiratory tract, the alveolar sacs, where gas exchange takes place, and the pleural linings surrounding the lungs are sites of these asbestos-related diseases. The spectrum of asbestos-related diseases ranges from nonspecific effects caused by any inhaled irritant, to fibrosis or scarring by collagen deposition, to cancer. The clinical and pathological features of these diseases will be summarized briefly below. The neoplastic diseases specifically associated with exposure to asbestos fibres will be emphasized. Pathological reactions associated with exposure to other natural and man-made fibres will be included, where this information is available.

Airway diseases. The major airways of the lower respiratory tract are the site of chronic bronchitis and chronic limitation of airflow, which are caused by persistent inflammation and excess mucus secretion. These are nonspecific reactions to various pollutants, including noxious gases, particulates and cigarette smoke. In the smaller, more distal airways, particulates accumulate in the walls of the terminal respiratory bronchioles. This is also a nonspecific reaction that occurs in cigarette smokers. These airway diseases cause increased morbidity, but they are not usually lethal (Becklake, 1994).

Asbestosis. Diffuse, bilateral interstitial fibrosis is the thickening of the walls of the alveolar sacs by increased deposition of connective tissue. Similar to the airway diseases associated with asbestos exposure, this pattern of fibrotic scarring of the lungs is nonspecific and occurs in response to a variety of insults to the alveoli. Asbestosis is characterized by fibrosis in the subpleural regions of the lower lobes of the lungs. Histopathological examination of lung tissue reveals the presence of asbestos bodies – fibres coated with haemosiderin, protein and mucopolysaccharides. Asbestosis is a progressive disease with clinical signs and symptoms developing after 10 or more years of

Table 1. Human diseases associated with asbestos exposure

Malignant diseases[a]	Non-malignant diseases[b]
Lungs	
Bronchogenic carcinoma	Asbestosis Asbestos-related small airway disease Major airway diseases: chronic bronchitis, chronic airflow limitation
Pleura	
Diffuse malignant mesothlioma	Effusion Pleural plaques Diffuse visceral pleural fibrosis Rounded atelectasis

[a]Churg & Green, 1995.
[b]Becklake, 1994.

repeated exposure to asbestos fibres. The disease was more prevalent in the past when exposures were several orders of magnitude greater than current exposures. Those affected gradually develop shortness of breath and impaired gas exchange leading to the inability to work, respiratory failure, heart failure (cor pulmonale) and premature death (Craighead *et al.*, 1982). Patients with asbestosis are at high risk of developing bronchogenic carcinoma, especially if they smoke cigarettes (Churg & Green, 1995); however, a causal relationship between fibrosis and bronchogenic carcinoma has not been established.

Bronchogenic carcinoma. Lung cancer arises from the epithelial lining of the large and small airways of the lungs. In most populations, cigarette smoking is the most common cause of lung cancer. Both nonsmokers and smokers exposed to asbestos fibres may develop bronchogenic carcinoma, although the risk is greatly increased in smokers. Similar to asbestosis, there is a latent period of at least 10–20 years between exposure to asbestos and the clinical manifestations of bronchogenic carcinoma. These cancers are associated with persistent cough, recurrent pneumonia, bleeding, weight loss or symptoms associated with metastatic spread. Bronchogenic carcinomas frequently metastasize early; survival beyond two to five years is rare (Cagle, 1995). Environmental exposure to erionite fibres has also been associated with the development of bronchogenic carcinoma (IARC, 1987a).

It is hypothesized that a single epithelial cell precursor gives rise to the four major histological types of bronchogenic carcinoma: small-cell carcinoma, large-cell carcinoma, squamous-cell carcinoma and adenocarcinoma (Cagle, 1995). An important subtype of adenocarcinoma is bronchiolo-alveolar carcinoma because it has unique clinical and pathological characteristics; these tumours arise in the periphery of the lungs and they may be multifocal. The incidence of bronchiolo-alveolar carcinoma appears to be increasing. This type of lung cancer frequently occurs adjacent to a peripheral, fibrotic scar; it has been described as 'scar carcinoma' (Barsky *et al.*, 1994). However, histopathological studies suggest that this type of cancer does not arise in a pre-existing scar; rather it stimulates a host fibrotic or desmoplastic reaction leading to retraction of the pleura overlying the growing neoplasm (Barsky *et al.*, 1986). This is an important observation because fibrous scarring is considered to be a predisposing factor for lung cancer in workers exposed to asbestos. The relationship between fibrosis and carcinogenesis will be discussed below (see *Mechanisms of fibre carcinogenesis*). Previously, adenocarcinomas were thought to be more common in asbestos workers than other histological types of lung cancer; however, most pathologists now agree that all histological types of lung cancer occur in association with asbestos exposure (Mollo *et al.*, 1990; Cagle, 1995).

Specific histological lesions develop in the respiratory epithelium prior to the appearance of a malignant carcinoma. These lesions are described as metaplasia, hyperplasia, atypical hyperplasia, dysplasia and carcinoma *in situ*. Specific genetic alterations may be identified in these pre-neoplastic lesions (Cagle, 1995); the specificity of these genetic changes in relationship to asbestos and cigarette smoking will be discussed below (*see Mechanisms of fibre carcinogenesis*).

Non-malignant pleural diseases. A monolayer of flat mesothelial cells covers both the surface of the lungs (visceral pleura) and the inner chest wall and the diaphragm (parietal pleura). Both of these layers of the pleura are affected by exposure to asbestos fibres, although the mechanism responsible for these reactions is unknown. The most common reaction to asbestos fibres is parietal pleural plaque. This is a fibrotic scar that develops on the lateral chest walls or on the superior surface of the diaphragm. These scars may become calcified and therefore visible on a chest X-ray, usually after 20–30 years of occupational asbestos exposure. People living in environments where asbestos fibres are present in the soil or near asbestos mines and industries also develop parietal pleural plaques (Bignon, 1989). Some physicians consider parietal pleural plaques to be biomarkers of asbestos exposure and a warning signal that these workers are at a higher risk of developing subsequent malignant complications (Hillerdall, 1994).

Less commonly, asbestos workers develop recurrent episodes of fluid accumulation in the space between the visceral and parietal layers of the pleura; this is called pleural effusion or benign

asbestos pleurisy. The fluid may compress the lungs and require drainage, and in some patients, may lead to diffuse fibrosis or scarring of the visceral pleura. Rounded atelectasis is a focal area of compression and collapse of the lung parenchyma due to an adjacent fibrous scar of the visceral pleura. Although none of these lesions is a precursor of a malignant neoplasm, these fibrotic pleural lesions may impair normal lung function (Schwartz, 1991).

Malignant pleural disease. Diffuse malignant mesothelioma is a lethal neoplasm arising from the pleura, the peritoneum or, rarely, the pericardium or tunica vaginalis of the testis (Churg & Green, 1995). The routes of translocation of asbestos fibres to these sites are unknown, although Oberdörster (1994) discusses experimental evidence for lymphatic dissemination of amphibole fibres. Approximately 80–85% of mesothelioma cases are associated with a history of occupational exposure to asbestos, especially to amphibole asbestos. Malignant mesothelioma has the longest latent period of all of the asbestos-related diseases – up to 50–60 years after the first exposure. No other known cofactors contribute to this malignant neoplasm; in contrast to bronchogenic carcinoma, there is no increased incidence in cigarette smokers (Churg & Green, 1995). Pleural plaques and malignant mesothelioma have also been found in people exposed to asbestiform fibres, especially erionite, or to tremolite in the environment (reviewed by Bignon, 1989).

Malignant mesothelioma arising in the pleural lining usually presents clinically as a diffuse mass encasing the lung in the presence of a bloody pleural effusion. There may be local invasion of the lung or chest wall, followed by metastases via the lymphatic system or bloodstream. Most patients have an extensive tumour mass upon diagnosis and suffer from difficulty in breathing, chest pain, weight loss, cough and fever (Musk & Christmas, 1992). Surgical resection of the tumour is difficult and malignant mesothelioma is resistant to chemotherapy and radiation. Few patients survive more than one to two years (Churg & Green, 1995).

Malignant mesotheliomas have a wide range of histological patterns; they can resemble epithelial carcinomas or fibroblastic sarcomas or a mixture of both. Pathologists must be careful to distinguish between a primary epithelial type of malignant mesothelioma and a metastatic adenocarcinoma. A variety of specialized tumour markers are used to aid in this difficult differential diagnosis (Henderson *et al.*, 1992). Specific molecular markers (see *Molecular alterations in asbestos-related neoplasms*) may eventually be useful in the diagnosis of primary malignant mesothelioma. In most patients, this neoplasm has reached an advanced stage at the time of clinical diagnosis; therefore, no specific histopathological precursor lesions have yet been identified. Examination of the pleural surfaces by thoracoscopy is a newer technique that may lead to identification of specific precursor lesions and earlier diagnosis of this neoplasm in workers exposed to asbestos (Boutin & Rey, 1993). These recent investigations provide evidence that mesothelioma may arise from the parietal pleura.

Other malignant diseases. Asbestos fibres have been found as contaminants of water and beverages; this observation leads to the possibility that this contamination may contribute to carcinomas of the gastrointestinal tract. Multiple epidemiological studies have not provided strong evidence for this association (reviewed in Bignon, 1989). In general, there is no accepted relationship between asbestos exposure and neoplasms other than bronchogenic carcinoma and malignant mesothelioma (Churg & Green, 1995).

In-vitro and in-vivo models

A variety of in-vitro and in-vivo experimental models have been developed to study the pathogenesis of asbestos-related diseases (see Tables 2 and 3). The accompanying reviews in this volume summarize recent experimental data obtained from these models; the limitations of these in-vitro and in-vivo model systems are discussed (see Consensus Report). Recent reviews of the in-vitro and in-vivo effects of man-made fibres have been published (Wheeler, 1990; Ellouk & Jaurand, 1994).

A central issue in extrapolating results from in-vitro to in-vivo models is the determination of the dose delivered to the target tissue. Investigators are now beginning to express dose in terms of fibre number rather than mass; a further improvement would also be the determination of the number of

Table 2. In-vitro models developed to study the pathogenesis of asbestos-related dieases

Model	Endpoints
Cell-free models	DNA damage Lipid peroxidation
Target cell populations[a]	Cell toxicity and apoptosis Release of inflammatory mediators Genotoxicity Transformation Cell proliferation Metaplasia Gene expression Intercellular communication

[a]Macrophages; lung epithelial cells; lung fibroblasts; mesothelial cells; organ cultures.

fibres delivered to target cells *in vitro* (Oberdörster, 1994) or *in vivo* (MacDonald & Kane, 1986). However, extrapolation of the dose delivered to target cells in these experimental models to the dose delivered to humans exposed to natural and man-made fibres is a major challenge (McClellan & Hesterberg, 1994).

Future epidemiological studies of workers exposed to recently developed fibres will be limited by the following factors. First, there will be no adequate epidemiological studies with sufficient latency. Second, the levels of exposure to these man-made fibres will almost certainly be lower than past exposures to asbestos and the worker populations are likely to be smaller. Therefore, it will be necessary to rely on experimental data based on in-vitro and in-vivo models in future evaluations of natural and man-made fibres.

Table 3. In-vivo models developed to study the pathogenesis of asbestos-related diseases

Model	Endpoints
Short-term animal models	Fibre deposition Inflammation Cell proliferation Pre-neoplastic changes
Long-term animal models	Lung and pleural fibre burdens Fibrosis Tumours Molecular and cytogenetic alterations

Classification and characterization of fibres that are known or potential carcinogens for humans

Classification of natural and man-made fibres

Fibrous minerals are divided into two major categories: asbestos and asbestiform (see Table 4). Asbestos is a term used to describe hydrated fibrous silicates, although the crystalline structure of serpentine asbestos is different from that of the amphiboles (IARC, 1977). Three types of asbestos fibres are used commercially: chrysotile, amosite and crocidolite. The other amphiboles may be present in chrysotile, vermiculite or talc mines. Three types of asbestiform fibres are used commercially: attapulgite, sepiolite and wollastonite (for more details see: Bignon, 1989; IARC, 1987a). People are exposed to the asbestos and asbestiform fibres that are used commercially; exposure to natural deposits of these fibres at the soil surface also occurs in the general population, even in rural areas. The magnitude of non-occupational exposures to natural fibres is usually very low and difficult to quantify (Bignon, 1989).

Many man-made fibres have been produced that resemble natural asbestos and asbestiform fibres in their geometry and flexibility, although man-made fibres do not generally split longitudinally. Man-made fibres are classified as vitreous or crystalline (see Table 5) and vary considerably in their chemical composition, strength, temperature resistance and durability. Fibres have also been derived from organic sources and their potential pathogenicity should also be assessed (Davis, 1992).

IARC evaluations of fibres as carcinogens

The experimental evidence for asbestos and asbestiform fibres as human carcinogens was evaluated by IARC working groups in 1977 and 1987 (IARC, 1977, 1987a,b, 1988; see Table 6). All forms of asbestos, talc containing asbestiform fibres and erionite fibres were evaluated as known human carcinogens (Group 1). Other naturally occurring fibrous

silicates were placed in Group 3 (not classifiable). Since these IARC evaluations, occupational exposure to anthophyllite has been associated with the development of diffuse malignant mesothelioma (Meurman *et al.*, 1994). The evidence for the carcinogenicity of five types of man-made vitreous fibres (MMVF) was evaluated by an IARC Working Group in 1988. Glasswool, rockwool, slagwool and ceramic fibres were placed in Group 2B (possibly carcinogenic to humans); glass filaments were placed in Group 3 (not classifiable).

Recognition of the diseases associated with past exposure to asbestos fibres raises concern about the potential carcinogenicity of other natural and man-made fibres. As of 1989, at least 70 different types of man-made fibres had been developed (Bignon, 1989). Since the previous IARC classifications of natural (IARC, 1977, 1987b) and man-made fibres (IARC, 1988), new experimental data have been obtained about the potential mechanisms of asbestos carcinogenesis. Concurrently, the procedure of IARC working groups has been modified to consider more explicitly certain mechanistic information in the assessments of the carcinogenic risk of agents for humans. Examples of mechanistic data that can be used in the evaluations are genotoxicity, effects on gene expression, cellular and tissue interactions and evidence of time and dose relationships in multistage models of carcinogenesis (Vainio *et al.*, 1992). Recent experiments that have provided new mechanistic data relevant to fibre carcinogenesis are summarized in the accompanying authored papers in this volume. The amount of experimental data available has expanded considerably since 1989, and these data have also provided important information about the physico-chemical properties of fibres that may contribute to their biological activity. Identification of these critical physico-chemical parameters may provide clues about the mechanisms responsible for fibre carcinogenicity.

Table 4. Classification of natural fibres[a]

Asbestos	Asbestiform
Serpentine	**Fibrous clays**
Chrysotile	Palygorskite (attapulgite)
	Sepiolite
Amphiboles	**Other fibrous silicates**
Actinolite	Wollastonite
Amosite	Nemalite (fibrous brucite)
Anthophyllite	Talc
Crocidolite	Zeolites:
Tremolite	• mordenite
	• erionite

[a]Modified from Bignon, 1989.

Properties of fibres relevant to biological activity

Dimensions. Fibre length was the first physico-chemical property to be associated with the carcinogenic potential of various natural and man-made fibres. This observation was reported by Pott and Friedrichs (1972) and by Stanton and Wrench (1972) using a rat model of malignant mesothelioma produced by direct intraperitoneal or intrapleural injection of fibres. Fibres longer than 8 μm in length and thinner than 0.25 μm in diameter were found to be more potent in inducing mesothelioma than shorter fibres of the same chemical composition (Stanton *et al.*, 1981). Although this conclusion has been debated (for example, by Dunnigan, 1984; Goodglick & Kane, 1990), most investigators agree that long fibres are more carcinogenic than short fibres. The mechanism responsible for the increased

Table 5. Classification of man-made fibres

Vitreous (MMVF)[a]
Glasswool
Glass filaments
Rockwool
Slagwool
Ceramic fibres
Crystalline[b]
Alumina
Graphite
Potassium titanate
Silicon carbide
Sodium aluminum carbonate
Synthetic zeolites
Organic
para-Aramid
Cellulose

[a]IARC, 1988.
[b]Modified from Leineweber, 1980.

Table 6. IARC evaluations of the strength of the evidence from human and experimental animal data for the carcinogenicity of fibres

Agent	Evidence from		Overall evaluation[a]
	Humans	Animals	
Asbestos[b,c]	Sufficient	Sufficient	1
Silicates[d]			
Wollastonite	Inadequate	Limited	3
Attapulgite	Inadequate	Limited	3
Sepiolite	No data	Inadequate	3
Talc			
• not containing asbestiform fibres	Inadequate	Inadequate	3
• containing asbestiform fibres	Sufficient	Inadequate	1
Erionite	Sufficient	Sufficient	1
Man-made vitreous fibres (MMVF)[e]			
Glasswool	Inadequate	Sufficient	2B
Glass filaments	Inadequate	Inadequate	3
Rockwool	Limited	Limited	2B
Slagwool	Limited	Inadequate	2B
Ceramic fibres	No data	Sufficient	2B

[a]1, the agent is carcinogenic to humans; 2B, the agent is possibly carcinogenic to humans; 3, the agent is not classifiable as to its carcinogenicity to humans.
[b]Asbestos: all forms – actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite.
[c]IARC, 1977, 1987b.
[d]IARC, 1987a.

potency of long fibres is unknown; Jaurand (1989) summarizes the following hypotheses:

- short fibres are phagocytized more readily by macrophages and thereby cleared more efficiently from the lungs;
- long fibres are incompletely phagocytized and trigger the release of more reactive oxygen/nitrogen species (ROS) than do short fibres;
- long fibres interfere with mitosis and chromosome segregation in dividing target cell populations.

These mechanisms will be reviewed in detail subsequently. Fibre diameter is also postulated to be an important parameter in carcinogenicity; for example, the transformation of Syrian hamster embryo cells (SHE) *in vitro* is sensitive to fibre diameter as well as fibre length (Hesterberg & Barrett, 1987).

Rodents were subsequently exposed to sized preparations of asbestos fibres by inhalation, and these experiments also confirmed the importance of fibre length in inducing pulmonary fibrosis and tumours (reviewed by Davis, 1994). The exact length of fibres responsible for these pulmonary reactions is uncertain. However, longer fibres are considered to be important in the pathogenesis of bronchogenic carcinoma based on the observation that fibres longer than 10 µm preferentially deposit at large airway bifurcations in casts of human airways (Sussman *et al.*, 1991). In animal inhalation studies and in humans exposed to fibres by inhalation, fibre dimension is a critical parameter in respirability. The dimensions of respirable fibres varies between humans and different species of experimental animals, and this variation must be considered in the design and interpretation of animal inhalation studies (McClellan & Hesterberg, 1994). Fibre dimension also contributes to biopersistence in the lung, as discussed below.

Chemical composition. Magnesium and iron, respectively, are important cations of the crystalline framework of serpentine and amphibole types of asbestos (IARC, 1977; Leineweber, 1980). Surface

magnesium ions are removed from chrysotile asbestos by acid-leaching *in vitro* or more slowly by progressive leaching *in vivo*; this alteration in cation composition has been observed to decrease the cytotoxicity and carcinogenicity of chrysotile asbestos (Monchaux *et al.*, 1981). The extent of chemical leaching of chrysotile in human lungs is controversial (Churg, 1994). Ferric and ferrous cations are major components of the crystalline lattice of amphibole asbestos fibres; iron may also be present as surface impurities on serpentine asbestos, amphiboles or some man-made fibres. The availability of iron at the surface of fibres is a critical parameter in catalysing the generation of ROS (reviewed by Fubini, 1993). Asbestos and other mineral fibres such as erionite may release or acquire iron from the surrounding medium, depending on the presence of chelators or reducing agents (Hardy & Aust, 1995; Eborn & Aust, 1996). The potential role of the iron-catalysed generation of ROS in asbestos-related cancers will be discussed below (see *Mechanisms of fibre carcinogenesis*).

Surface reactivity. Surface area is an important parameter that contributes to the surface reactivity of fibres. The unique structure of fibres such as erionite greatly increases their surface area; internal 'cages' in erionite and synthetic zeolites function as cation exchangers (Leineweber, 1980). Chemical composition, surface charge and surface area also influence the ability of fibres to adsorb exogenous or endogenous molecules. Surface adsorption of exogenous compounds such as polycyclic aromatic hydrocarbons (PAH) may be important in the pathogenesis of bronchogenic carcinoma, as discussed below. Adsorption of endogenous macromolecules such as lung surfactant or immunoglobulins may alter the biological reactivity of fibres (Scheule & Holian, 1989), and lipids, proteins and DNA may also adhere to the surface of fibres (Ellouk & Jaurand, 1994).

Durability and biopersistence. Durability is an important characteristic of fibres that are used commercially. Durability is usually assessed by dissolution *in vitro*. Biopersistence describes the overall retention of fibres in the respiratory tract, and includes mechanical clearance, dissolution and leaching. This is a complex process dependent on the local extracellular and intracellular environment. Fibres may split longitudinally or transversely after deposition in the lungs. Splitting of chrysotile fibres may initially increase the number of fibres in the lungs (Davis, 1994); however, eventually, the reduced length of the fibres increases their rate of clearance. Clearance also depends on lung fibre burden, as described recently for refractory ceramic fibres (Yu *et al.*, *1994*). The chemical composition and surface architecture of MMVFs were shown to be altered dramatically after chronic inhalation in rats (Hesterberg *et al.*, 1994). In contrast, in this same model, refractory ceramic fibres were altered less in rats and hamsters (Mast *et al.*, 1994). Other fibre types such as wollastonite have been shown to persist for very short periods after short-term inhalation by rats (Warheit *et al.*, 1994). Amphibole fibres persist longer than chrysotile in human lungs (reviewed by Case, 1994; Churg, 1994). Few studies have investigated the persistence of man-made fibres in people. According to Sébastien (1994), glass fibres may be less persistent than chrysotile fibres. There are insufficient data for mineral wool or ceramic fibres, but one study reports prolonged persistence of silicon carbide fibres (Sébastien, 1994).

The physical and chemical modification of fibres in the lungs is hypothesized to reduce their biopersistence and biological reactivity (reviewed by Davis, 1994; De Vuyst, 1994). However, certain caveats have been raised about this generalization. First, the following 'hot spots' of prolonged fibre persistence have been proposed: (i) sites of lymphatic drainage in the parietal pleura (De Vuyst, 1994); (ii) airway bifurcations (Lippman, 1994); and (iii) within areas of fibrosis (Davis, 1994). Second, different fibre types or modified fibres may alter the mobility of macrophages and the translocation of fibres towards the pleura or lymph nodes (Davis, 1994). Finally, Barrett (1994) warns that no relationship has been established between biopersistence of fibres in the lung and the induction of genetic and epigenetic changes that may lead to cancer.

It is important to consider these caveats in the interpretation of internal fibre dose (which is measured as the number of fibres that persist in the lungs – the lung fibre burden – at the time of diagnosis of disease or at autopsy of exposed people). Although this information is important, especially